variation (90% confidence interval, –18% to +18%), and the interobserver coefficient of variation is also fairly high.[11] Thus the prediction power of troponin T, which in a way is a biochemical marker of LV mass, may reflect residual confounding attributable to the fact that LV mass is measured imprecisely by echocardiography. In other words, adjustment for LV mass might not take away the whole effect of this factor. On the other hand, in biological terms, troponin provides information that goes beyond LV mass and function, because the plasma concentration of this substance reflects myocardial-cell distress. Thus it may also be that the good prediction power of troponin T depends on the fact that this biomarker adds relevant biological information (myocardial-cell distress) to that provided by echocardiographic measurement of LV mass. As is mentioned above, the fact remains that this biomarker, independently of the nature of the link between plasma troponin and circulatory overload, emerges as a most promising prognostic factor for this outcome in PD patients.

Validation of a biomarker is a complex process[1] that also requires appropriate studies testing whether measurement of the biomarker is useful in clinical practice. The United States Food and Drug Administration approved the measurement of troponin T in dialysis patients for risk stratification. However, a prospective, randomized clinical trial testing the value of troponin in a clinical decision-making context is still needed to solidly establish the place of this biomarker in everyday clinical practice in ESRD patients. For example, should these patients be intensively treated by a pharmacological approach, or should they be considered for coronary revascularization even in the absence of symptoms? The study by Wang *et al.*[4] offers an important new piece of evidence on the potential usefulness of troponin T in asymptomatic PD patients and makes even more compelling the case for prospectively testing treatment policies that incorporate this biomarker in the management of these patients.

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Myostatin and insulin-like growth factors in uremic sarcopenia: the yin and yang in muscle mass regulation

RH Mak[1] and P Rotwein[2]

Myostatin and the insulin-like growth factors (IGF-I and -II) play inhibitory and stimulatory roles, respectively, in the development and regulation of skeletal muscle mass. The findings of Sun *et al.* in this issue shed light on the potential regulation and actions of this yin-and-yang system in uremic sarcopenia and the salutary effects of exercise.

Kidney International (2006) **70**, 410–412. doi:10.1038/sj.ki.5001622

Myostatin (also known as growth/differentiation factor-8) is a member of the transforming growth factor-β family that plays an essential role in the regulation of skeletal muscle mass. Myostatin is expressed initially in the myotomal compartment of developing somites and continues to be expressed in muscle throughout development and in adult animals. Mice with a targeted disruption of the myostatin gene display a marked increase in muscle mass, up to three times normal size, as a result of a combination of muscle fiber hyperplasia and hypertrophy. The myostatin sequence has been highly conserved throughout evolution. Remarkably, the human, rat, mouse, porcine, turkey, and chicken proteins are identical in the biologically active COOH-terminal portion of the molecule. The function of myostatin as an inhibitor of skeletal

[1]*Department of Pediatrics, Oregon Health & Science University, Portland, Oregon, USA; and* [2]*Department of Biochemistry and Molecular Biology, Oregon Health & Science University, Portland, Oregon, USA*
Correspondence: *RH Mak, Department of Pediatrics, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Mail Code NRC5, Portland, Oregon 97201-3098, USA; E-mail: makr@ohsu.edu*

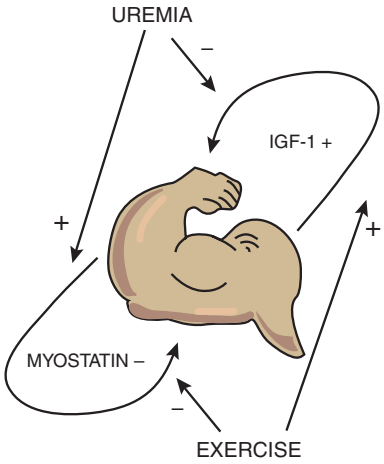

Figure 1 | Myostatin (–) and IGF-I (+) modulation of muscle mass and the effects of uremia and exercise.

muscle growth also appears to be conserved across species. A frameshift mutation, caused by an 11-nucleotide deletion in the third exon of the gene, which eliminates virtually all of the region encoding the mature portion of the myostatin molecule, has been linked to the 'double muscling' phenotype in Belgian blue cattle, which is characterized by a generalized increase in muscle mass. Another apparently spontaneous mutation in the myostatin gene in a child is also associated with enormous muscle hypertrophy.[1]

In addition to local actions in skeletal muscle during development, myostatin may have endocrine functions in adult animals. Myostatin circulates in a latent form that can be activated by acid treatment. Indeed, systemic overexpression of myostatin in adult mice induced profound muscle and fat loss analogous to that seen in human cachexia syndromes. Thus, myostatin may act as a muscle 'chalone,' a term proposed over 30 years ago for a circulating protein that inhibits the growth of a particular tissue and thereby maintains appropriate tissue mass.[2]

Insulin-like growth factor-I (IGF-I) and IGF-II are essential for embryonic and postnatal development of skeletal muscle and other tissues. Mice engineered to lack IGF-I or the IGF-I receptor were significantly smaller than their control littermates and had reduced muscle tissue, whereas transgenic mice with targeted overexpression of IGF-I to muscle showed increased muscle mass.[3] Additionally, IGF-II expression has been positively associated with skeletal muscle development in double-muscled cattle and in pig breeds with exceptional muscle mass.[4] *In vitro*, IGFs inhibit apoptosis and can promote the proliferation and differentiation of skeletal muscle cells.[3] In rodents, work overload (WO) has been shown to cause muscle hypertrophy by activating intracellular signaling pathways that are linked to local production of IGFs by growth hormone-independent mechanisms.[5] The less severe stimulus of repetitive exercise also promotes muscle growth, and this adaptive response can be enhanced in transgenic mice expressing IGF-I in muscle,[6] and prevented in mice with a dominant-negative form of the IGF-I receptor targeted to muscle.[7] Thus, the beneficial effects of exercise on muscle are mediated at least in part through paracrine actions of local IGF-I.

Cachexia, presenting as sarcopenia (disproportionate muscle wasting), is reported to have a prevalence of 30%–60% in patients with end-stage renal disease and contributes to both mortality and morbidity in these individuals. Loss of skeletal muscle mass and strength is probably the most important factor regulating survival in patients with end-stage kidney disease, since with severe muscle atrophy critical physiological functions are significantly impaired. Substantial muscle loss also contributes directly to asthenia and to the reduction in physical activity and quality of life seen in end-stage renal disease. The molecular mechanisms causing uremic sarcopenia are not well understood, although the etiology is multifactorial and includes contributions from inflammation, anorexia, increased metabolic rate, acidosis, and resistance to anabolic hormones such as growth hormone and IGF-I.

Sun and colleagues[8] (this issue) showed that WO, produced by experimental unilateral gastrocnemius tendon ablation, corrected uremic sarcopenia. In the atrophied uremic muscle, basal myostatin mRNA levels were increased significantly but were reduced toward normal values after WO, suggesting a role for myostatin in the wasting process. WO led to a rise in muscle IGF-I mRNA levels and IGF-I protein expression in both uremic and pair-fed control rats. On the other hand, stimulation of IGF-I expression by growth hormone was severely attenuated in uremic rats compared with controls. Thus, WO could bypass the growth hormone resistance seen in uremia and could restore IGF-I expression in muscle in association with correction of uremic muscle atrophy. In the aggregate, these findings provide insight into mechanisms of skeletal muscle wasting in uremia by linking it to enhanced myostatin expression, and they additionally demonstrate that the anabolic response to local WO remains intact in uremia, as do the molecular pathways promoting work-induced IGF-I gene and protein expression. In addition, the observations of Sun *et al.*[8] suggest that less severe stimulus of exercise also may promote positive energy balance in muscle through stimulation of local production of IGF-I and inhibited expression of myostatin (Figure 1).

The significance of the findings of Sun and colleagues[8] to human renal disease is not clear. In a recent study of sedentary well-nourished maintenance hemodialysis patients, Wang *et al.*[9] showed that myostatin mRNA levels in skeletal muscle were similar to values in normal control subjects. The differences in myostatin gene expression noted in uremic rats with sarcopenia and seen in hemodialysis patients in the study by Wang *et al.* may reflect the fact that the human subjects were well nourished and had no clinical evidence of muscle wasting. Indeed, nutritional parameters such as body mass index, percentage body fat, skin-fold thickness, and muscle circumference did not differ from those of healthy controls. Furthermore, these patients had normal appetites and had little evidence of systemic inflammation, as indicated by normal C-reactive protein concentrations. It is also possible that species differences are contributing to the divergent results. In a previous study, myostatin could be detected in the blood in mice but not in humans.[2]

Despite these caveats, the clinical implications of this study are significant. Exercise in the form of endurance or resistance training may suppress muscle myostatin expression and may reverse or limit sarcopenia. In a preliminary report, myostatin mRNA levels were decreased after prolonged endurance exercise training in dialysis patients.[10] Thus exercise may well be an important adjunct therapy in these

individuals. Clinical studies are thus much needed to examine the differential benefits of endurance versus resistance training for sarcopenia, for inflammation, and for overall mortality and morbidity in patients with end-stage renal disease. In addition, further investigation into the molecular pathogenesis of uremic cachexia and sarcopenia may reveal novel therapeutic targets for preventing these potentially life-threatening complications.

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Dendritic cells: Not just another cell type in the kidney, but a complex immune sentinel network

C Kurts[1]

Dendritic cells (DCs) are crucial for inducing and regulating adaptive immunity. These cells also exist in the kidney, where, however, their function had been unknown. A study by Soos *et al.* now demonstrates that renal DCs form an intricate cellular network that continuously surveys the tubulointerstitium, and reveals a previously unrecognized immune sentinel system of the kidney.

Kidney International (2006) **70**, 412–414. doi:10.1038/sj.ki.5001613

Dendritic cells (DCs) represent one of the most extensively studied topics in immunology, because of their central role in the induction and regulation of adaptive immunity, and because of their therapeutic potential for manipulating immune responses. Most of our knowledge of their physiology was extrapolated from *in vitro* studies, or from *in vivo* analysis of the secondary lymphatics and the skin, where DCs are copious and relatively easily accessible. Yet even so, DCs reside in virtually all tissues, including the kidney. Despite their obvious potential to contribute to renal inflammation, these cells have received relatively little attention so far. This may now change, as novel transgenic mouse strains have become available that greatly facilitate their observation *in vivo*. This issue of *Kidney International* features a study by Soos *et al.* that used such a mouse strain to reveal an intricate network of DCs that appear to patrol the renal tubulointerstitium (Figure 1).[1] The complexity of this network is surprising. Evidently, the DCs residing in the kidney form an immunosurveillance network whose extent has not been fully appreciated yet.

The principal DC function is the induction of adaptive immune responses, in particular those executed by T cells. Their bone marrow-derived precursors enter from the bloodstream as immature DCs. These migrate through tissues, collect antigens, and sense 'danger' signals (pathogen-derived molecular patterns, tissue damage, local inflammation). Such signals induce DC maturation, which results in the loss of phagocytic activity and expression of co-stimulatory molecules and enhances migration to draining lymph nodes, where naive T cells await activation. Activated T cells leave the lymph nodes in search of the antigen source — for example, infectious pathogens which they can combat either directly or indirectly by stimulating other immune effectors, such as macrophages. In the absence of pathogens, DCs will remain immature and fail to upregulate co-stimulatory molecules. Autoantigens carried by such immature DCs will tolerize autoreactive T cells. In this way, DCs also maintain peripheral self-tolerance. Whether these fundamental principles that have been demonstrated for DCs in the skin, intestine, pancreatic islets, lungs, or liver apply also to renal DCs is mostly unknown.

Our lack of knowledge about renal DCs is partially due to technical difficulties in detecting and isolating these fragile cells from the kidney. Thus, the first convincing evidence for their existence was provided not earlier than in 1994, when Kaissling and Le Hir observed by electron microscopy numerous tubulointerstitial cells with DC morphology.[2] In the same year, Austyn, Roake, and colleagues reported functional major histocompatibility complex class II$^+$ expression by these cells and their ability to induce T-cell allo-activation.[3]

[1]*Institute of Molecular Medicine and Experimental Immunology, Friedrich-Wilhelms-Universität, Bonn, Germany*
Correspondence: *C Kurts, Institute of Molecular Medicine and Experimental Immunology, Friedrich-Wilhelms-Universität, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany. E-mail: CKurts@uni-bonn.de*